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Appl. No. 09/847,102
Amdt. dated February 1, 2007
Amendment under 37 CFR 1.116 Expedited Procedure
Examining Group 1642

PATENT**REMARKS/ARGUMENTS**

With this amendment, claims 1-8, 16, and 28-29 are pending. Claims 9-15 and 17-27 are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in the October 24, 2006 Office Action.

I. Rejections under 35 U.S.C. §112, first paragraph, written description

According to the Office Action, claims 1-8, 16, 28 and 29 are rejected because the claims contain subject matter that was allegedly not described in the specification in a manner to convey that the inventors had possession of the claimed invention at the time of filing. The Office alleges that the claims introduce new matter. The Office Action further alleges that the following claim limitations are not supported by the specification as filed: "the antibody inhibits growth of the malignant cell that expresses the frizzled 5 receptor" (claim 1) and "wherein the antibody is effective for immunotherapy of malignant cell that overexpresses the frizzled 5 receptor" (claim 28). The Office Action does indicate that original claims 1 and 10 provide support for an antibody that binds to SEQ ID NO:68 and modulates a biological activity of a malignant cell that expresses a frizzled 5 receptor. *See, e.g.*, Office Action at page 2.

The position of the Office Action is in clear disagreement with both case law and US Patent Office Rules. "It is now well accepted that a satisfactory description may be in the claims or any other portion of the originally filed specification." MPEP 2163 (page 2100-166), *citing In re Koller*, 204 USPQ 702 (CCPA 1980); accord *In re Gardner*, 177 USPQ 396 (CCPA 1973); accord *In re Wertheim*, 191 USPQ 90 (CCPA 1976). The MPEP also states that "information contained in any one of the specification, claims or drawings of the application as filed may be added to any other part of the application without introducing new matter." MPEP 2163.06. If necessary, Applicants can amend the specification to include material disclosed in an originally filed claim. *Id. citing In re Benno*, 226 USPQ 683 (Fed. Cir. 1985).

Original claim 1 recites "A purified antibody for modulating a biological activity of a malignant cell that expressed a frizzled receptor, wherein said antibody binds to at least one epitope in an extracellular domain of the frizzled receptor expressed in the malignant cell."

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Claim 10 depends from claim 1 and recites SEQ ID NO's: 61, 63, 64, 66, 68, 69, 71, 73, 75, and 77 as the extracellular domain of the frizzled receptor. The specification defines modulation of a biological activity of a malignant cell that expresses a frizzled receptor at page 22, lines 3-6: "... the term 'modulating a biological activity of a malignant cell' refers to the ability of the antibody to effect cellular function. These effects may manifest themselves as cell growth inhibition, the ability to elicit a cytotoxic response to the malignant cell, or other such negative effects on the malignancy." As a dependent claim, claim 10 includes all the limitations of claim 1 for each individual recited SEQ ID NO. The limitations include "modulating a biological activity of a malignant cell" as defined in the specification at page 22, lines 3-6, *e.g.*, "cell growth inhibition, the ability to elicit a cytotoxic response to the malignant cell, or other such negative effects on the malignancy." Thus, the specification as filed provides support for an antibody that binds to SEQ ID NO:68 and inhibits growth of a malignant cell that expresses the frizzled 5 receptor. If necessary, Applicants stand ready to amend the specification at page 22, lines 3-6 to recite the Frizzled antigens listed in claim 10. Similarly, example 5 at page 28 of the specification discloses overexpression of the Frizzled 2 receptor in malignant cells and clearly states that Frizzled 2 is exemplary for other frizzled antigens. Therefore, the amendment of the claims cited in the Office Action does not introduce new matter. In view of these arguments, withdrawal of the rejection for alleged lack of written description is respectfully requested.

II. Rejections under 35 U.S.C. §103(a)

Claims 1-8, 16 and 28-29 are rejected under 35 U.S.C. §103(a) as allegedly obvious over of Tanaka *et al.*, *Proc. Natl. Acad. Sci. USA* 95:10164-10169 (1998) in view of US Patent No. 5,677,171 (Hudziak *et al.*). Applicants respectfully traverse. The Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the

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claims limitations. MPEP§2143. See also *In re Rouffet*, 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999).

The claims are directed to antibodies that bind to the amino terminal extracellular domain of the frizzled 5 receptor, and that inhibit growth of a malignant cell that expresses the frizzled 5 protein. Using the frizzled 2 protein as an example for the class of frizzled proteins, Applicants were the first to demonstrate that antibodies directed against a frizzled protein extracellular domain are sufficient to inhibit proliferation of a malignant cell that expresses the frizzled protein.

Tanaka *et al.* disclose expression of seven frizzled genes in esophageal cancer cells and matched normal esophageal cells. Based on the observed expression pattern, Tanaka *et al.* reach conclusions only about the expression of FzdE3 gene product and no other frizzled gene product. The Office Action at page 4 alleges that this disclosure of Tanaka *et al.* is similar to that of the instant specification. This is incorrect. Tanaka *et al.* provide no disclosure that an antibody directed against a frizzled protein extracellular domain is sufficient to inhibit proliferation of a malignant cell that expresses the frizzled protein. Tanaka *et al.* provide no suggestion that an attempt to inhibit malignant cell proliferation using a frizzled antibody would be successful. In contrast, the specification demonstrates as an example for the class of frizzled proteins, that antibodies against a frizzled 2 extracellular domain inhibit proliferation of malignant cell lines that express frizzled 2.

None of the cited references provide evidence that the frizzled 5 protein is differentially expressed in malignant cells. The data presented in Tanaka *et al.* shows that expression of frizzled 5 is not correlated with esophageal cancer (see, e.g., Figure 1). Moreover, at Figure 1 Tanaka *et al.* disclose only amino acids 250-322 of the frizzled 5 protein. Tanaka *et al.* do not teach or suggest use of the amino terminal domain of frizzled 5 (SEQ ID NO:68,

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amino acids 1-235) as an antigen for frizzled 5 antibody production. Thus, Tanaka *et al.* fail to disclose the claimed amino terminal extracellular frizzled 5 sequence and, in fact teach away from a role for frizzled 5 in cancer.

The Office Action alleges that Tanaka *et al.* discloses that ectodomains of frizzled proteins function as a "natural antagonist" of frizzled mediated signal transduction and that frizzled proteins are receptors for "Wnt oncoproteins". Thus, the Office Action assumes that all wnts and frizzled proteins have assigned functions. As discussed in a previous response, this is not correct. The arguments are maintained but are not repeated here. Tanaka *et al.* does not provide a suggestion that the frizzled 5 protein or its ligand are oncogenic.

The Office Action also cites Hudziak *et al.* as providing motivation "to screen an antibody binding to the extracellular domain . . . of frizzled 5 protein, which is expressed on a malignant cell as taught by Tanaka *et al.*, wherein the antibody inhibits the growth of the malignant cells since the screening assay is taught by Hudziak patent." Office Action at page 5. This statement misinterprets the results of both Tanaka *et al.* and Hudziak *et al.* to produce an unsupported motivation to combine the references. Hudziak *et al.* place two conditions on producing antibodies that could have similar properties to the disclosed HER2 antibodies: antibodies that bind a growth factor receptor or ligand and inhibit the growth factor receptor biological function and tumor cells that express the growth factor receptor and depend on the receptor's biological function for cell growth. Hudziak *et al.* at column 5, lines 39-47. Nowhere does Hudziak *et al.* teach or suggest that all growth factor receptors will be required for growth of a tumor cell or that all antibodies against growth factor receptors will inhibit growth of a tumor cell. Hudziak *et al.* also fail to teach that any frizzled protein is a growth factor receptor.

On reading Tanaka *et al.*, those of skill would understand that frizzled proteins, including FzE3 and frizzled 5, do not meet the conditions set by Hudziak *et al.* Tanaka *et al.* do not demonstrate that FzE3 function, or any other frizzled protein function, is required for growth of esophageal cancer cells. Tanaka *et al.* did not produce any antibodies against the FzE3 protein and did not demonstrate that antibodies against FzE3 can inhibit growth of a cancer cell. The

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first recognition that antibodies against frizzled proteins can be used to inhibit growth of malignant cells that express frizzled proteins is found in the instant specification.

Thus, alone or in combination, the cited references do not provide a motivation or reasonable expectation of success in generating frizzled 5 antibodies that inhibit growth of a malignant cell. Therefore, the cited references cannot render the claimed antibodies obvious.

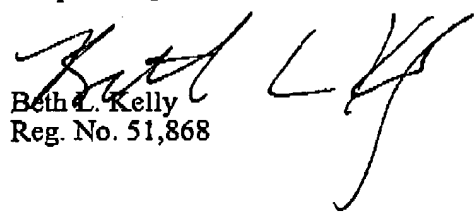
In view of the above arguments, withdrawal of the rejections for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,


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